ABBOTT

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September 15, 1999

The Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane Room 1061
Rockville, MD 20857

RE: Comments on the FDA's Proposed Rule: Supplements and Other Changes to an Approved Application
[Docket No. 99N-0193]

Dear Sirs or Madams:

Abbott Laboratories submits the following remarks in response to the Agency's request for comments on the above-named subject and docket. Abbott is an integrated worldwide manufacturer of healthcare products employing more than 56,000 people and serving customers in more than 130 countries.

EXECUTIVE SUMMARY

The FDA has proposed withdrawing the current 21 CFR 314.70 and replacing it with a new proposal published on June 28, 1999. The proposed rule generates new requirements for filing regulatory submissions, adds new categories for filing those submissions and increases the documentation burden on industry. While some categories contained in the proposal provide additional clarity and relief, firms are basically left with new requirements for regulatory submissions.

Abbott generally supports the detailed comments submitted to the Agency from the Parenteral Drug Association (PDA) and from the Pharmaceutical Research and Manufacturers of America (PhRma). However it should be noted that considerable differences in the comments from these and other organizations lead us to believe that the proposal may ultimately be in need of further development and discussion between the various parties. The Agency's considerable amount of work to develop this proposed rule and the draft guidance on this subject is noteworthy. While we believe this is a significant proposal, we are willing to help or participate in developing these documents further.

99D-0529

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A. General Remarks

1. *Reporting Requirements.* One goal of FDAMA was to reduce the overall reporting requirements for manufacturers, and the combination of regulation and guidance was supposed to allow for flexibility in the reporting requirements. Yet in summary we believe that the proposal places new and additional reporting burdens on industry. One specific concern is the increased use of prior approval supplements (PAS) which, if enacted as proposed, would place additional resource requirements on both the Agency and on industry. With this prospect in mind, the Agency should consider using the remaining categories of regulatory supplements to a much greater degree.

2. *Validate.* The FDA's use of the word "validate" throughout the proposal might be confused with the CGMP definition; therefore, we suggest alternate words such as "assess," "study," or "evaluate."

3. *Sterilization.* The FDA has added this new category of PAS for "changes that may affect sterility assurance," and within that category there are 11 new criteria for submitting a PAS. This seems excessive and perhaps redundant when one considers the many existing and draft guidances which already cover sterilization.

4. *Lapsing of the Current 21 CFR 314.70.* The Agency should issue a written explanation or hold a public meeting to discuss the impact of allowing the current statute to expire without a new rule being formally approved. However, the lack of a formal statute should not allow a proposed rule to be implemented without adequate public comment and review.

5. *Relationship With USP.* In several places, e.g., proposed 21 CFR 314.70 (b) and (c), the Agency appears to be altering the reporting relationship between the United States Pharmacopoeia and the Food and Drug Administration. To obtain additional clarity and direction on this matter, we believe that these changes should be formally addressed either in writing or at a public meeting.

6. *Relationship with Other Guidance Documents.* The broad scope of the draft guidance document and the proposed rule brings in to question the relationship of these proposals to both current guidance documents and those guidances which are waiting to be finalized. For example, some additional detail should be provided regarding the stability guidance document and the guidance on container-closure systems. Their relationship with the SUPAC and BACPAC documents should also be clarified.

B. Specific Comments

Specific comments are attached here in Table 1.

C. Closing Remarks

The final rule should be implemented through a "phasing in" of the regulation in order to educate industry and Agency reviewers on the new expectations. The final promulgation and implementation of the proposed rule should be undertaken in conjunction with an industry-wide educational effort for the following reasons:

1. General educational purposes. Due to the cost and broad scope of this proposal, any seminars or public workshops on the final rule will help everyone concerned and allow for additional input from all affected parties. The proposed seminars could be carried out with the support of FDLI, AFDO, HIMA, or other scientifically-oriented trade associations. The Agency should also consider a telecast similar in format to the FDLI's presentation on latex which was held on May 5, 1998. The agenda for this broadcast was developed through a consensus-based approach and drew upon the collective expertise of the FDA and industry.

2. Publicity. The impact of this proposed rule will affect regulatory practices and expectations of manufacturers. By carrying out these seminars, the Agency can publicize and prepare all concerned for the new requirements.

3. Clarity. Finally, public seminars will serve to clarify regulatory expectations and interpretations.

Yours truly,

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cc: Eric B. Sheinin (HFD-800)
Robert A. Yetter (HFM-10)
[Docket No. 99D-0529]

Enclosure

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Table #1

Abbott Laboratories Comments on:
Proposed Rule "Supplements and Other Changes to an Approved Application" (Docket No. 99N-0193); and Draft FDA Guidance "Changes to an Approved NDA or ANDA" (Docket No. 99D-0529)
Table of Specific Comments
August 27, 1999

Comments on 21 CFR 314.3

Section	314.3 Regulation Line	Guidance Line Cross-Reference	Comment	Rationale
Proposed Rule	(b)	496-499; 865-868	Delete "intermediates, raw materials, reagents, and other components including container closure systems and in-process materials." It is recommended that changes for these materials be handled separate from this regulation/guidance.	This definition is not consistent with ICH Q6A, wh includes only API and drug product (DP). To inclu items beyond the API and DP in this guidance represents a level of complexity that would be bett dealt with in later guidances that can adequately evaluate the significance of changes to specific iten including a more in-depth FDA/Industry dialogue. There exists a potential for confusion and some ma agree with current guidance (e.g., BACPAC).
Proposed Rule	(a)(5)	---	Clarify whether the field copy that is to be sent to the applicant's "home FDA district office" should be the FDA office where the change is being made or the FDA office in the district of the company's corporate headquarters from where the submission documents are sent. Also, if it should be sent to the office where the change is being made, clarify what FDA office(s) serve for changes made internationally (outside the USA).	Clarification will help to ensure that the appropriat documents get to the right FDA district office.
Proposed Rule	(b)(2)(iii)	370-410; 433-444; 447-465	Delete lines. Replace with "Changes that reduce the sterility assurance level".	The impact on sterility assurance level should be th guiding factor in any change. As proposed, the verbiage is too broad and if interpreted conservativ would be overly burdensome in terms of regulatory reporting.
Proposed Rule	(b)(2)(v)	716	Clarify "labeling..." to "drug product labeling...".	API labeling changes should not need be submitted the registration.

Section	314.70 Regulation Line	Guidance Line Cross-Reference	Comment	Rationale
Proposed Rule	(b)(3)(viii); (d)(3)(iii)	---	Delete reference to SOPs. Delete "The date each change was made, a cross reference to relevant validation protocols and/or SOPs, and" and the word "(validation)".	This data represents compliance information and is better suited for field inspections. The addition of this information to existing practice would result in increased regulatory burden. The fact that the annual report changes were made during the NDA's annual reportable year should be sufficient information; more specific timing will be available at the manufacturing site in appropriate GMP documentation available for inspection.
Proposed Rule	(b)(4)	62-68	Feedback to Sponsor on acceptance or refusal of "Expedited Review" Request within 30 days.	Currently the CFR includes the provision for "Expedited Review", however, there is no mechanism for communication of acceptance or refusal on expedited review request
Proposed Rule	(c)(2)(ii)(B), (d)(2)(iii)	471-473; 481-482	Clarify equipment that is "similar, but not identical" versus equipment of the "same design and operating principal." [Follow Equipment Addendum to various SUPAC Guidances]	Similar/but not identical classifies as a CBE-30, but same design/operating principal is annual reportable; but the difference is not readily apparent. No references under MAJOR changes (Rules) addressing equipment changes, this section may be addressing the "gray" area under SUPAC for equipment of the same operating principle (class) but different design (subclass). The Rule, therefore may have missed the MAJOR change of different operating principle/design that is caught in the Draft Guidance found starting with Line 408. For equipment changes, which are of different operating principle and design – consider Major category. Changes in equipment which are of the same operating principle but different design – consider Moderate change.

Section	314.70 Regulation Line	Guidance Line Cross-Reference	Comment	Rationale
Proposed Rule	(c)(6)(ii)	638-639	Add "a sterile drug product, or a sterile drug substance" to read "...container for a nonsterile drug product, except for solid dosage forms, a sterile drug product, or a sterile drug substance without a change...".	Size and shape changes for sterile API and drug products have only moderate potential impact. This especially true when the nature of the size/shape changes are very minor in nature, as is often the case when suppliers make minute adjustments in their packaging components.
Proposed Rule	(d)(2)(i)	522-523; 567-571	Change to "Any change made to comply with an official compendium."	Section 501(b) of the FD&C Act requires the FDA t resolve any differences with the compendial body, th USP. It is unfair to place the applicant in the middle of these discussions, and the compendial review process should be the mechanism via which the FDA has influence. In addition, it should be permitted an appropriate that any USP-adopted changes, includin changes that may relax acceptance criteria and/or analytical procedures, be updated via an annual repo Such an updated process would apply to both the innovator as well as any generic companies.
Throughout the proposed rule and guidance	---	---	Clarify and standardize use of "drug product," "drug," and "product." Change "drug substance" to "active pharmaceutical ingredient" to be consistent with other guidances. Clarify if "product" includes API or not.	Terminology changes throughout the document can lead to confusion of interpretation.
II. Reporting Categories	54-56	---	The Guidance should expand on those areas of hardship based on unforeseeable circumstances that may necessitate expedited review.	Catastrophic circumstances is too limiting. There ar other situations beyond the applicant's control wher the Agency could partner with the applicant to assur continued supply to the patient. For example, a serie of situations were cited by the Agency during an FDA/FDLI telecast titled "Case Studies."
Same	64-68	(b)(4)	FDA should identify time limits for review of an applicant's response to a notification within the 30 day window.	If the review time is left unspecified, then it effectiv becomes PA supplement, just because more information is requested. Suggest if response is with the 30 day window, FDA should stick to original 30 day limit. If response comes in afterward, then another 30 day window is established. This would b similar to the IND review process during the 30 day wait period.

III. General Requirements	89	(a)(6)	For annual reports this section should refer to a summary introduction of the CMC section instead of cover letter.	There presently is no requirement for a cover letter t an annual report under 314.81.
B. Equivalence	155-157	---	Change "of the drug product" to "of the material produced at the processing step where the change is made or at a subsequent step."	Equivalence is demonstrated at the processing step where the change is made or at a subsequent step. According to BAPAC I, equivalence may be demonstrated at a drug substance intermediate, and does not require assessment of the drug product.
Same	271-276	---	Move "refurbished" and "different aseptic processing facility" to CBE-30. (Keep "newly constructed" as prior approval for the first product).	The ability to move parenteral operations between different manufacturing facilities which have a satisfactory parenteral cGMP inspection should represent no additional regulatory burden over that f non-sterile products.
Same	285-291		A move to a site on a different campus or changes within a single facility or same campus for the manufacture of drug substances or drug product should be reported within an annual report.	Since the requirement for a satisfactory cGMP inspection will have already been met, the process is not changing, and FDAMA requires prior 'validatio such changes represent minimal risk and should be annual reportable.
Same	303-309	---	Delete "same or". Only a move to a different campus should require a Changes Being Effected Supplement.	A non-sterile drug product may be moved within the same site (i.e., building change) in an annual report (see lines 319-322). To require a Changes Being Effected Supplement for drug substance intermediat is excessive.
VI. Sites D. Minor Changes	317	---	Delete sentence.	Currently, locations of testing sites within a laborato are not identified. New testing site could be to a adjacent laboratory bench which should not require annual report notification.
Same	333-334	---	Modify example to "Change in the floor plan which results from a facility "build out."" Move example under example "4."	Change in verbiage eliminates unnecessary reporting of insignificant changes to floor plans and concentra on facility build out. Currently, room location or flo plans are not identified in registrations. The propos verbiage would require that continuous GMP improvements be reported, adding additional reporti burden. Format change would flow better after the example for same campus changes.
Same	335-336	---	Delete example "Improvements to manufacturing areas that provide greater assurance of quality."	This example represents a GMP compliance issue th should be regulated by the field if at all.

VII. Manufacturing Process A. General Considerations	347-351; 591-595	---	Delete these lines. Inference is that the applicant is not able to adequately evaluate the potential adverse effects of a change.	The burden of risk falls on the applicant to appropriately validate the effects of the change. The applicant has the most first-hand knowledge of the issues for a product/process, and per the original validation work included in the initial (A)NDA, shou be granted the scientific technical ability to evaluate the change. In cases where applicants have demonstrated a lack of technical ability, special remedies should be sought rather than penalizing all firms.
Same	357	(b)(2)(iii)	Delete or narrow the phrase "(2) changes may affect product sterility assurance".	Statement is too broadly worded and similar to lines 370-401; 433-444, and 447-465 could be interpreted suggest an overly burdensome level of additional regulatory reporting requirements.
Same	370-401; 433-444; 447-465	(b)(2)(iii)	Delete all lines. The list of changes that may affect product sterility assurance is overly extensive and not appropriate for this general guidance. (1) Changes in many of these criteria should be maintained as cGMP documentation at the manufacturing sites and available for inspection by the agency. For example, changes in equipment (lines 380-383), changes in sterilizer load configurations (lines 398-399), changes in dry heat depyrogenation systems (lines 435-437), changes to filtration parameters (lines 438-444) are all cGMP issues that should be covered during compliance inspections. (2) Add "Changes that reduce the sterility assurance level." in place of lines 370-401. (3) Add "Changes that provide the same or better sterility assurance level." in place of lines 433-444 and lines 447-465. A good example of a change providing better assurance is the replacement of an aseptic fill area with an isolator system. (4) Add bullet for "Change from sterile filtered or aseptic processing to terminal sterilization, or vice versa." after line 414.	The list of sterile process/product changes present ar overly burdensome level of additional regulatory reporting. (1) For many of the changes, the appropriate cGMP documentation of the impact on sterility assuran may be more quickly evaluated by compliance specialists in the field than by causing an implementation delay with submission preparati and approval. (2 and 3) The impact on the sterility assurance level (SAL) should be the guiding factor in any chang If the change reduces SAL, a prior approval submission is warranted. A lower reporting leve (e.g., CBE-30) should be permissible if the applicant has adequately validated the process ar shown that the change provides an equivalent or better SAL. (4) This type of major manufacturing change represents a good example of a fundamental cha in the manufacturing process or technology for a parenteral drug product.
Same	402- 407; 468-473	(b)(2)(vii) (c)(2)(ii)	Delete these requirements for natural products.	These new requirements add additional regulatory burden from that of current reporting requirements without expressed justification or definition.

Same	408	---	Clarify the phrase "Any fundamental change in the manufacturing process". The phrase is too vague and all-encompassing, even with the examples provided. Also consider providing parenteral examples.	The broad scope of the verbiage will lead to confusion.
Same	413	---	Clarify that 413 applies only to drug products and not APIs.	N/A
Same	491	---	Add "or lyophilized" dosage forms.	Change in order of addition of ingredients for lyophilized dosage forms should have no different impact than solution dosage forms.
Same	501-504	---	Clarify that production environmental controls (e.g., environmental monitoring for particulates and/or microorganisms) are GMP in nature and not specifications requiring regulatory submissions.	Although provided initially in registrations via the sterilization validation package, these production controls are considered GMP in nature and should be handled via FDA compliance.
VIII. Specifications C. Moderate Changes	538	---	Change to "Any changes in a regulatory analytical procedure for which the change significantly impacts the method validation package." Also change this example to CBE versus CBE-30.	• Minor revisions are often made in regulatory analytical procedures (e.g., typographical corrections, clarifications, analyst safety precautions). • Development of a good AM-PAC guidance would be the best way forward here.
VIII. Specifications D. Minor Changes	567-571	(d)(2)(i)	Change to "Any change made to comply with an official compendium."	Section 501(b) of the FD&C Act requires the FDA to resolve any differences with the compendial body, the USP. It is unfair to place the applicant in the middle of these discussions, and the compendial review process should be the mechanism via which the FDA has influence. In addition, it should be permitted and appropriate that any USP-adopted changes, including changes that may relax acceptance criteria and/or analytical procedures, be updated via an annual report. Such an updated process would apply to both the innovator as well as any generic companies.
Same	573-576	---	Delete "that provides....in the approved application."	For alternative analytical procedures, the applicant carries the burden of proving that it provides the same or greater level of control. Therefore this phrase is more of a definition of the term and is thus redundant.
IX. Package A. General Considerations	586-713	---	This section categorizes packaging changes based on providing examples of very specific changes for the various dosage forms. While the examples cover many of the changes typically needed from a post approval	Packaging changes are often the most scientifically straightforward of pharmaceutical changes. Decision trees based on drug product interaction and container/closure protective properties provide a

			perspective, they fall short and as technology and processes improve, the guidance will quickly become outdated. Changes should be categorized based on the potential for interaction with DP and change in the protective properties of the container/closure system in context of the dosage form.	science-based approach to regulatory change assessment. The examples proposed represent an increase in the regulatory burden for packaging post approval changes in some areas and reduction in others. There is a very obvious disconnect in the approach of this guidance and the Packaging Guidance recently issued.
X. Labeling	717	---	Some guidelines around the requirement to "PROMPTLY revise all promotional labeling" might be helpful. For example, (consistent with past FDA practice) significant safety or efficacy revisions should be made within 30 days, less significant revisions within 60-90 days. Minor revisions at the time of the next printing.	N/A
Same	736-7	---	Change 7. to "Change to a less restrictive labeled storage condition, unless exempted by regulation or guidance."	Changes to more restrictive storage conditions, should not require prior approval.

HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CROSS REFERENCE SHEET

Docket Number/Item Code: 99N-0193/C30

See Docket Number/Item Code: 99D-0529/C37

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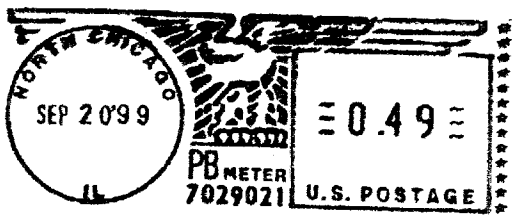

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